Medical and Pediatric Oncology 26:238–243 (1996)

Acquired Von Willebrand Disease in Children With a Wilms' Tumor

Anne B. Jonge Poerink-Stockschläder, MD, Ina Dekker, Inge M. Risseeuw-Appel, MD, and Karel Hählen, MD, PhD

The association between acquired von Willebrand disease and Wilms' tumor has been reported in eight cases: four case reports and one prospective study of Coppes et al. [J. Clin Oncol 10:422–427, 1992] who found this in four out of 50 patients. We retrospectively studied 73 children who were diagnosed with a Wilms' tumor between 1970 and 1993. All patients were treated according to the running international SIOP protocol. According to our local diagnostic workup protocol, blood samples for screening coagulation tests were obtained at diagnosis and during preoperative chemotherapy. Since 1984, factor VIII analysis was added. In four patients, no coagulation screen was done. Bleeding time and screening tests apart from APTT were normal in all 69 children tested before or within 2 days after starting therapy. In 47 out of 73 patients, an APTT was performed *before* starting therapy. In 19 patients (40%), it was prolonged (>33 sec). In 8 of them (17%), the prolongation was severe (≥40 sec). In 11 out of the 19 patients, factor VIIIc, factor VIIIag, and factor VIII RcoF determinations were done. In two children, all three factors were decreased suggestive for von Willebrand disease. One of the 19 patients with a prolonged APTT had hematuria. The others had no increased bleeding tendency or signs of bleeding in the tumor. In all patients, the prolonged APTT normalised during preoperative chemotherapy within 6 weeks. Frequent blood samples were obtained of the two children with acquired von Willebrand disease and showed normalisation of the coagulation disorder after 1 and 2 weeks, respectively. No specific therapy to correct the coagulation abnormalities was given to any patient.

Key words: Wilms' tumor, acquired von Willebrand disease, prolonged APTT

INTRODUCTION

Von Willebrand disease (vWD) is an inherited autosomal coagulation disorder generally characterized by an increased bleeding tendency, especially mucocutaneous bleeding, prolonged bleeding time, abnormally low levels of factor VIII coagulant activity (factor VIIIc), von Willebrand factor (factor VIIIag), and ristocetin co-factor activity (factor VIII RcoF) [1,2]. However, not all of these features are necessarily present in every individual with this disorder [1].

Acquired von Willebrand disease has been reported in the literature repeatedly in association with lymphoproliferative disease [3–5], monoclonal gammopathies [3,6,7], myeloproliferative disorders [8–10], hypothyroidism [11–13], and Epstein Barr virus infection [14]. In a few case reports it has been associated with a solid tumor, e.g., adrenal cortical carcinoma [15] and Wilms' tumor [16–19]. In March 1992, Coppes et al. [20] reported four children with acquired von Willebrand disease in 50 patients with a Wilms' tumor.

Since we routinely obtained blood samples for coagulation screening in the workup of children with Wilms' tumor, we studied this association in our own patient population.

MATERIALS AND METHODS

The study included all 73 patients (31 boys, 42 girls) with a Wilms' tumor who were diagnosed between 1970 and 1993 at the Sophia Children's Hospital in Rotterdam. The age at diagnosis was 3 months to 12 years with a mean of 4 years. All patients were treated according to the running international SIOP protocol (SIOP 2, 5, 6, and 9).

In SIOP 2 and SIOP 5, 1 week of vincristin and actinomycin combined with 2 weeks of tumor-directed abdom-

From the Department of Pediatrics, Division of Hematology/Oncology, Sophia Children's Hospital/University Hospital, Erasmus University, Rotterdam, The Netherlands.

Received August 2, 1994; accepted March 10, 1995.

Address reprint requests to K. Hählen, M.D., Sophia Children's Hospital/University Hospital, Erasmus University Rotterdam, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands.

inal radiotherapy were given preoperatively. In SIOP 6, preoperative chemotherapy with vincristin and actinomycin was given during 4 weeks, followed by tumornephrectomy and postoperative chemotherapy with vincristin and actinomycin. In SIOP 9, preoperative chemotherapy with vincristin and actinomycin and, depending on the stage of the tumor, adriamycin, was given for 4 weeks followed by tumornephrectomy. Depending on the stage of the tumor, different regimens of postoperative chemotherapy followed. In some children, particularly those <6 months, primary nephrectomy was done.

Medical history including family history and physical examination was done at diagnosis. According to our local diagnostic protocol, blood samples for screening coagulation tests (activated partial thromboplastin time = APTT, bleeding time = BT, normotest = NT, thrombotest = TT, prothrombin time (= Quick time) = PTT) had to be obtained at diagnosis and during therapy, in particular before surgery. In 1984, complete factor VIII analysis, including factor VIIIc, factor VIIIag, and factor VIII RcoF was added, because we noticed prolonged APTTs in a number of children. By then, two case reports [16,17] describing acquired von Willebrand disease in Wilms' tumor patients had been published, and determination of fVIII in small volumes of blood became possible in our laboratory. The blood samples had to be taken at diagnosis *before* starting therapy, 1 or 2 weeks after starting therapy, and just before the tumor nefrectomy (4–6 weeks after starting preoperative chemotherapy).

None of the patients received blood transfusions, platelet transfusions, or fresh frozen plasma prior to surgery. No specific therapy to correct the coagulation abnormalities was given.

Blood was drawn by venipuncture or from the infusion line in a peripheral vein (after discarding the first 5 ml) in cups containing 3.8% trisodium citrate. None of the children had a central line, and no heparin was used in the infusion line. The samples were chilled immediately in an ice bath and centrifuged at 20,000 rpm for 30 minutes at +4°C. The screening tests were done immediately; the remaining plasma was frozen and stored at −80°C. All coagulation determinations were done in triplicate with commercially available reagents and methods. The APTT was determined by using cefalin as the particulate activator. The NT and the TT were performed by a clotting assay with the Nyco-med reagent; the bleeding time was done according to the Ivy method. The factor VIIIc was done by an one-stage assay using commercial deficient plasma (Baxter). The factor VIIIag was determined quantitatively by the ELISA technique. The factor VIII RcoF was done by the platelet agglutination method (Behring).

For the diagnosis of acquired von Willebrand disease, all following criteria had to be met: (1) no previous bleeding disorder, (2) prolonged APTT (>33 sec), (3) decreased factor VIIIc (<80%), (4) decreased factor VIIIag (<60%), and (5) decreased factor VIII RcoF (<40%). Multimer analysis was not done.

RESULTS

In four patients, no coagulation screen at diagnosis was done. In 17 patients, only BT, NT, TT, and PTT proved to be performed, which were all within normal limits.

In five patients, the APTT was performed 1 or 2 days after starting therapy. Therefore, they were not considered further. In all these cases the APTT was within normal limits, as were the other screening tests.

In the remaining 47 patients, the screening tests, including an APTT, were performed at diagnosis before starting therapy. In 19 out of these 47 patients (40%), the APTT was prolonged (>33 sec). In eight of them, the prolongation was severe (≥40 sec). The other screening tests proved to be normal; in particular no prolonged BT was found in any patient. Five children happened to have two APTT determinations before starting treatment and had prolonged APTTs on both occasions.

Since complete factor VIII analysis was added after 1984, no such data are available in seven of the 19 patients with a prolonged APTT. In one patient, the sample for factor VIII analysis was obtained 1 day after starting therapy and proved to be normal. Thus in 11 out of the 19 patients with a prolonged APTT, a complete factor VIII analysis was done before treatment. In two patients, it revealed results consistent with von Willebrand disease according to our criteria.

The prolonged APTTs normalised after starting therapy in all patients. The two children with acquired von Willebrand disease were checked more frequently (see Table II). In the first patient, all coagulation studies became within the normal range within 1 week, in the second patient within 2 weeks. After starting chemotherapy, tumor reduction was achieved in all patients.

Only one of the 19 patients with a prolonged APTT had macroscopic hematuria. The others had no evidence of increased bleeding tendency. Medical history revealed no bleeding problems and physical examination was normal. The family histories revealed no increased bleeding tendency.

DISCUSSION

Our study reveals two observations not reported before in the literature. First, considering only the 47 patients in whom an APTT was measured before treatment, a high proportion (40%) of prolonged APTTs was found, whereas 17% was even severely prolonged. In the literature, the APTTs were mentioned only in relation to the reported cases of acquired von Willebrand disease and

were, as expected, prolonged in all of them (Table I). However, our study reveals that many children have a prolonged APTT while they have no acquired von Willebrand disease according to our criteria.

Second, without specific treatment, normalisation of the prolonged APTTs was found in all cases within 6 weeks after starting chemotherapy, prior to surgery. In all cases reported in the literature, however, FFP, DDAVP, or factor VIII concentrate was given to correct the coagulation disorders.

The bleeding time and screening tests apart from APTT were normal in all 69 children with Wilms' tumor tested before or within 2 days after starting therapy. The bleeding time is mentioned only in the descriptions of the eight reported children with acquired von Willebrand disease and is abnormal in six out of the eight cases (Table I). The finding of normal bleeding times even in children with prolonged APTT or acquired von Willebrand disease confirms the relative value of this test for the diagnosis of acquired von Willebrand disease [1,21].

In our study, 26 out of 73 patients are excluded due to a missing or late APTT test. This was due to a number of coincidences such as admittance of the patient during the weekend, APTT performed after starting treatment, "forgot" to send in blood for coagulation tests, or not being able to acquire enough blood for coagulation tests. It was never a "clinical" decision to omit coagulation tests.

The incidence of acquired von Willebrand disease in children with Wilms' tumor we found (2/47, 4%) to be comparable to that reported by Coppes et al. [20]. According to our criteria, patient numbers 3 and 4 in the Coppes et al. study (Table I) would have dropped out. In our series there were also two such children with decreased factor VIIIc and factor VIIIag, but with normal factor VIII RcoF, normal bleeding time, and an APTT of 33 sec and 37 sec, respectively. According to our criteria, these patients had no acquired von Willebrand disease.

Several hypotheses have been postulated to explain the acquired von Willebrand disease. Immunological inactivation was proposed by Handin et al. [5] who described an adult male with lymfosarcoma and von Willebrand disease. In the patient's plasma, the authors were able to demonstrate an IgG-type antibody that prevented aggregation of normal platelets by ristocetin [5]. In the study of Mannucci et al. [3], however, no such inhibitor could be demonstrated. In the single case reports of Wilms' tumor patients with acquired von Willebrand disease, all authors [16–19] looked for but failed to demonstrate an inhibitor. Assuming there is such an inhibitor, there might be less production of it after tumor reduction, leading to more functional von Willebrand factor, which could explain our findings of spontaneous normalisation of the coagulation disorder after starting therapy.

Absorption of the von Willebrand factor by tumor cells was suggested by Richard et al. [8], who demonstrated by indirect immunofluorescence that the von Willebrand factor was selectively absorbed into myelomatous cells in a patient with acquired von Willebrand disease in multiple myeloma.

Facon et al. [15] reported a patient with adrenal cortical carcinoma and acquired von Willebrand disease in which absorption of the von Willebrand factor by tumor cells was demonstrated also by indirect immunofluorescence. In Wilms' tumor patients, possible tumor absorption of the factor VIII molecular complex was ruled out only by Scott et al. [17]. If so, reduction of tumor cells could account for less absorption and consequently higher values of von Willebrand factor, which is in keeping with our findings.

Bracey et al. [19] suggested a confounding factor. In their patient with a Wilms' tumor, the coagulopathy was supposed to be secondary to hyperviscosity caused by elevated serum levels of hyaluronic acid. According to these authors, there was not a true decrease in factor VIII but an interference of the factor VIIIag assay with hyaluronic acid. Their conclusion was based on residual von Willebrand factor activity (factor VIII RcoF) in the complete absence of von Willebrand factor antigen (factor VIIIag). If a high level of hyaluronic acid is related with the volume of the tumor, reduction in size of the tumor may give lower levels of hyaluronic acid and less disturbance of the coagulation tests.

Whatever the theory, the bottom line is that tumor reduction is crucial for normalisation of the coagulation abnormalities. This is supported by the finding of persistent prolongation of the APTT before starting chemotherapy in five of our patients and by the normalisation of the coagulation tests after starting chemotherapy in all our patients. Tumor reduction was achieved in all our patients [22,23].

All patients with a Wilms' tumor should undergo a coagulation screen at diagnosis because there might be acquired von Willebrand disease. The coagulation screen should at least include APTT, BT, PTT, factor VIIIag, and fVIII RcoF. The APTT is important because it is prolonged in acquired von Willebrand disease even when the bleeding time is normal (Table II).

For the children who are treated according to SIOP protocols, the diagnosis of acquired von Willebrand disease has no clinical consequences at the time of diagnosis unless there is an increased bleeding tendency, because the SIOP protocol does not prescribe a histological diagnosis (biopsy) before starting preoperative chemotherapy. However, in case of surgery or severe bleeding, correction of the coagulopathy with DDAVP or fVIII concentrate is indicated [9,24].

For patients who are treated according to other treatment protocols like the NWTS protocol, which emphasizes early tumornephrectomy, it is important to know whether this coagulation abnormality exists before sur-

TABLE I. Clinical and Laboratory Features of Reported Cases of vWD and Wilms' Tumor*

	Haemorrhagic symptoms at presentation	BT (min, sec)	Normal range	APTT (sec)	Normal range	F VIIIc (%)	Normal range	F VIIIag (%)	Normal range	F VIII RcoF (%)	Normal range
Noronha et al. [15]	bruising, gingival bleeding	>20	<12	94.7	30–45	5	50–150	<2	60–185	ND	50–150
Scott et al. [16]	hematuria	8	2–6	82	37–50	18	60–150	<6	50–150	28	50–150
Han et al. [17]	none	5,3	<9	79	30–45	6	NG	4	NG	18	NG
Bracey et al. [18]	epistaxis	20	<5	38	≤35	37.3	55–145	U	NG	16.3	45–150
Coppes et al. [19]											
Patient no. 1	none	>20	2–7	52	25–40	10	50–150	4	50–150	8	60–150
Patient no. 2	none	18		46.8		10		<1		5	
Patient no. 3	none	9		44.7		27		4		46	
Patient no. 4	none	6		54.1		27		76		54	
Own patients											
Patient no. 1	none	4,15	2–6	47	28–33	13	80–130	25	60–140	<12	40–150
Patient no. 2	none	4,15		39		47		<12,5		27	

*Abbreviations: ND, not determined, NG, not given, U, undetectable.

TABLE II. Results of Coagulation Studies in Our Patients with Aquired vWD

	APTT (sec)	BT (min, sec)	F VIIIc (%)	F VIIIag (%)	F VIII RcoF (%)	Thrombocytes ($\times 10^9$/L)
Patient no. 1						
At diagnosis	47	4,15	13	13	<12	203
After 1 week of therapy	33	ND	122	104	36	157
After 2 weeks of therapy	33	ND	134	>180	144	438
Before operation	29	ND	76	80	111	ND
Patient no. 2						
At dia gnosis	39	4,15	47	<12.5	27	281
After 1 week of therapy	40	ND	121	79	171	358
After 2 weeks of therapy	31	ND	185	183	233	342
Before operation	27	4	ND	ND	ND	126
6 weeks after operation	31	ND	169	168	153	282

ND = not determined.

gery since unexpected major bleeding during surgery may occur [17,18].

In conclusion, a high proportion (40%) of the children with a Wilms' tumor showed a prolonged APTT at diagnosis. In 17%, there was even a severe prolongation. In only two patients (4%), acquired von Willebrand disease was found. All these coagulation disorders normalized without specific treatment after starting chemotherapy, probably as a result of tumor reduction.

A prospective study on the incidence and etiology of the acquired von Willebrand disease in Wilms' tumor patients is in progress to better characterize the clinical relevance of this coagulation disorder.

REFERENCES

1. Werner EJ, Abshire TC, Giroux DS, Tucker EL, Broxson EH: Relative value of diagnostic studies for von Willebrand disease. J Pediatr 121:34–38, 1992.
2. Bloom AL: Von Willebrand factor: Clinical features of inherited and acquired disorders. Mayo Clin Proc 66:743–751, 1991.
3. Mannucci PM, Lombardi R, Bader R, Horellou MH, Finazzi G, Besana C, Conard J, Samama M: Studies of the pathofysiology of acquired von Willebrand's disease in seven patients with lymphoproliferative disorders or benign monoclonal gammopathies. Blood 64:614–621, 1984.
4. Brownlee RE, Shockley WW: Acquired von Willebrand's syndrome. Arch Otolaryngol Head Neck Surg 117:106–108, 1991.
5. Handin RI, Martin V, Moloney WC: Antibody induced von Willebrand's disease: A newly defined inhibitor syndrome. Blood 48: 393–405, 1976.
6. Stewart AK, Glynn MFX: Acquired von Willebrand disease associated with free lambda light chain monoclonal gammopathy, normal bleeding time and response to prednisone. Postgrad Med J 66:560–562, 1990.
7. Harlé JR, Lefevre P, Pesquié M, Aillaud MF, Dalmasso C, Boucraut J, Gulian JM, Karsenti JM, Bernard D, Charrel M: Maladie de Willebrand acquise, cryoglobulinémie et pseudo-analbuminémie au cours d'une dysglobulinémie monoclonale. La Presse Médicale 19:1661–1664, 1990.
8. Richard C, Cuadrado MA, Prieto M, Batlle J, López Fernández MF, Rodriguez Salazar ML, Bello C, Recio M, Santoro T, Gomez Casares MT, Zubizarreta A: Acquired von Willebrand disease in multiple myeloma secondary to absorption of von Willebrand factor by plasma cells. Am J Hematol 35:114–117, 1990.
9. Thies K, Budde U, Hellstern P: Blutstillende Therapie bei einem Patienten mit erworbener von Willebrand Erkrankung und M. Waldenström mit Plasmaspherese und DDAVP. Beitr Infusionsther 26:179–182, 1990.
10. Tatewaki W, Shibata A: Acquired von Willebrand disease in patients with chronic myeloproliferative disorders. Leukemia Lymphoma 1:51–57, 1989.
11. Dalton RG, Savidge GF, Matthews KB, Dewar MS, Kernoff PBA, Greaves M: Hypothyroidism as a cause of acquired von Willebrand's disease. Lancet 2:1007–1009, 1987.
12. Blesing NE, Hambley H, Mc Donald GA: Acquired von Willebrand's disease and hypothyroidism: Report of a case presenting with menorrhagia. Postgrad Med J 66:474–476, 1990.
13. Coccia MR, Barnes HV: Hypothyroidism and acquired von Willebrand disease. J Adolesc Health 12:152–154, 1991.
14. Kinoshita S, Yoshioka K, Kasahara M, Takamiya O: Acquired von Willebrand disease after Epstein-Barr virus infection. J Pediatr 119:595–598, 1991.
15. Facon T, Caron C, Courtin P, Wurtz A, Deghave M, Bauters F, Mazurier C, Goudemand J: Acquired type II von Willebrand's disease associated with adrenal cortical carcinoma. Br J Hematol 80:484–494, 1992.
16. Noronha PA, Hruby MA, Maurer HS: Acquired von Willebrand disease in a patient with a Wilms' tunor. J Pediatr 95:997–999, 1979.
17. Scott JP, Montgomery RR, Tubergen DG, Hays T: Acquired von Willebrand's disease in association with Wilms' tumor: Regression following treatment. Blood 58:665–669, 1981.
18. Han P, Lou J, Wong HB: Wilms' tumor with acquired von Willebrand's disease. Aust Paediatr J 23:253–255, 1987.
19. Bracey AW, Wu AHB, Aceves J, Chow T, Carlile S, Hoots WK: Platelet dysfunction associated with Wilms' tumor and hyaluronic acid. Am J Hematol 24:247–257, 1987.
20. Coppes MJ, Zandvoort SWH, Sparling CR, Poon AO, Weitzman S, Blanchette VS: Acquired von Willebrand disease in Wilms' tumor patients. J Clin Oncol 10:422–427, 1992.
21. Drouin J, Lillicrap DP, Izaguirre CA, Sutherland M, Windsor S, Benford K, Hoogendoorn H, Giles AR: Absence of a bleeding tendency in severe acquired Von Willebrand's disease: The role of platelet Von Willebrand factor in maintaining normal hemostasis. Am J Clin Pathol 92:471–478, 1989.
22. Lemerle J, Voûte PA, Tournade MF, Rodary C, Delemarre JFM, Sarrazin D, Burgers JMV, Sandstedt B, Mildenberger H, Carli M, Jereb B, Moorman-Voestermans CGM: Effectiveness of preoper-

ative chemotherapy in Wilms' tumor: Results of an International Society of Paediatric Oncology (SIOP) clinical trial. J Clin Oncol 1:604–609, 1983.
23. Robben SGF, Meradji M, Tan IL, Hakvoort-Cammel FGAJ: Reduction of tumor volume in nephroblastoma and abdominal neuroblastoma by chemotherapy: An ultrasound study. Zentralblatt Radiologie. 144:642, 1991.
24. Rodheghiero F, Castaman G, Mannucci PM: Clinical indications for desmopressin (DDAVP) in congenital and acquired von Willebrand disease. Blood Rev 5:155–161, 1991.